PAIN RESEARCH
HEAL Initiative

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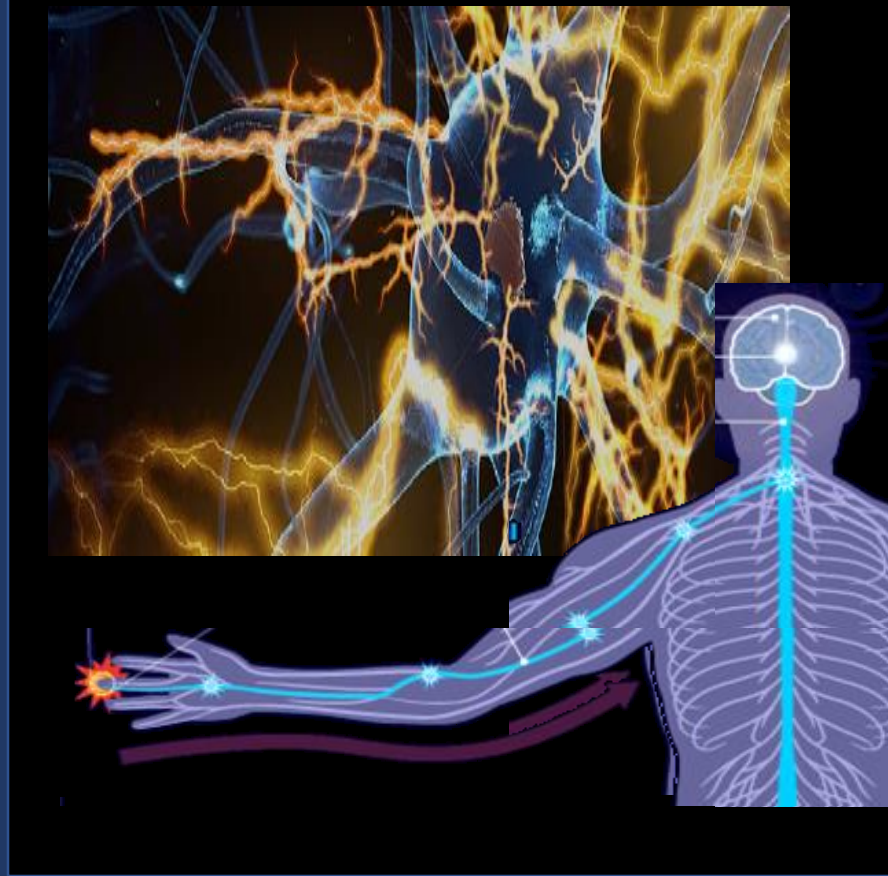
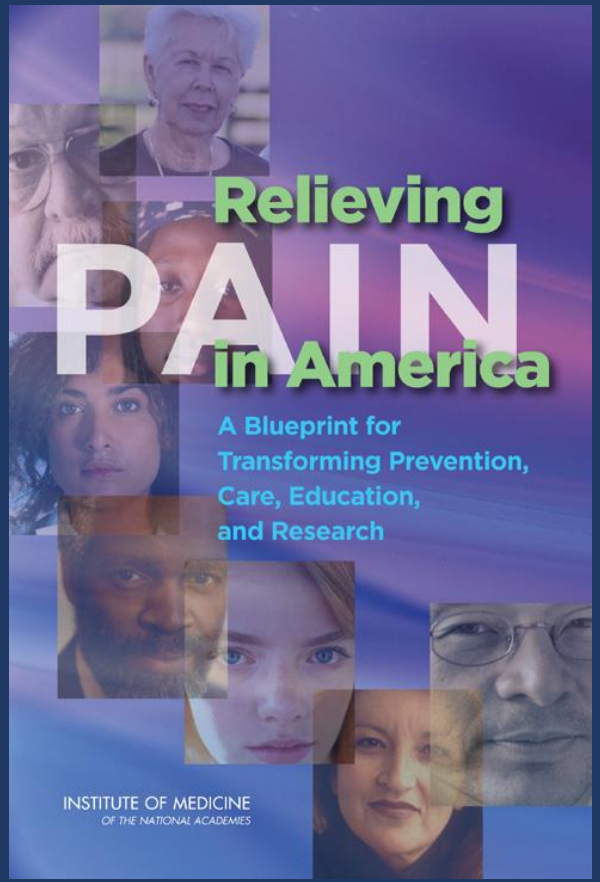
National Institute on Drug Abuse
@NIDAnews





National Institutes of Health
National Center for Complementary and Integrative Health

Pain in the U.S.

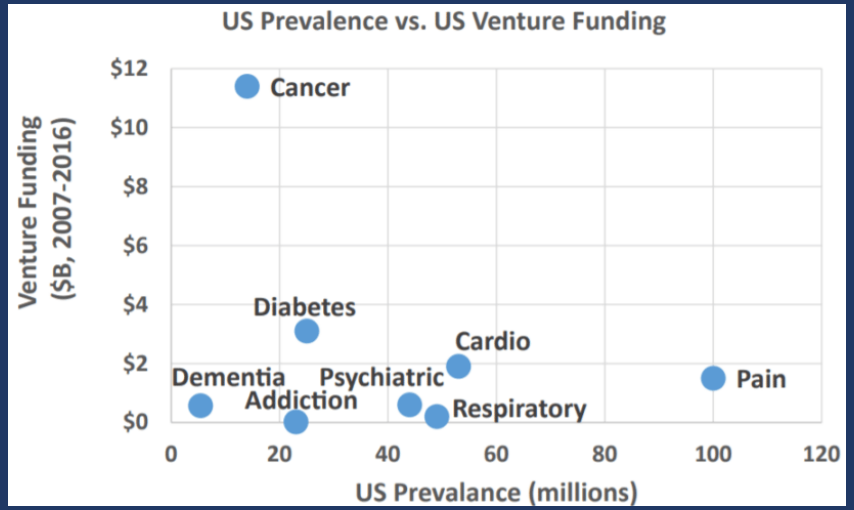
25.3 million
American adults suffer from daily pain

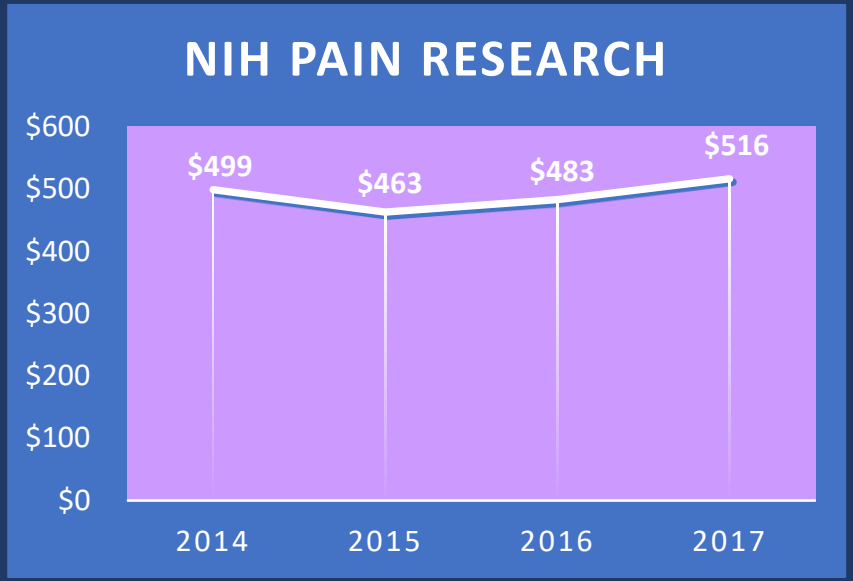
23.4 million
American adults report a lot of pain

Nahin RL. Estimates of Pain Prevalence and Severity in Adults: United States, 2012, *Journal of Pain* (2015), doi: 10.1016/j.jpain.2015.05.002.

What's with pain? Analysis shows scarce private investments, high failure rate

NIH investments on Pain Research





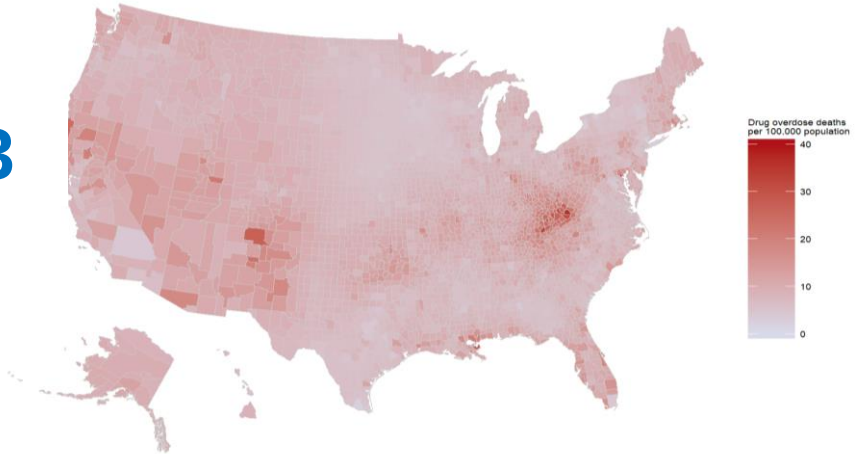
John Carroll Endpoints news, Feb 12 2018

THE CRISIS: NATIONAL OVERDOSE DEATH RATES

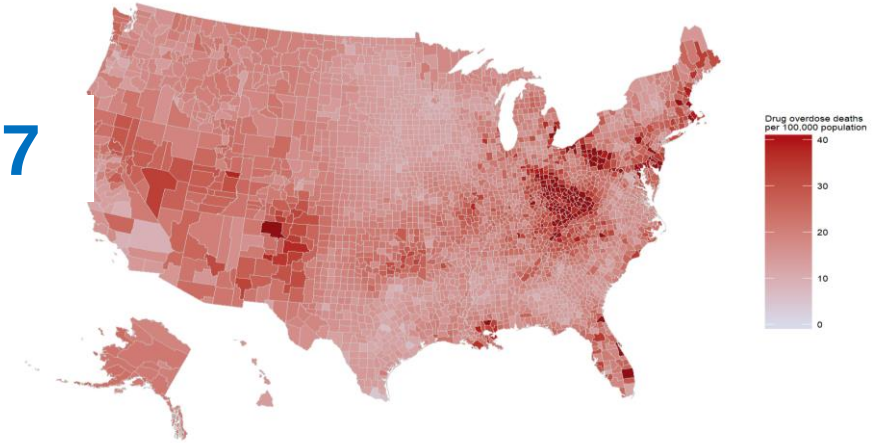
IN 2017, THERE WERE 70,237 OVERDOSE DEATHS (9.6% HIGHER THAN 2016)

Source: https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/index.htm

2003

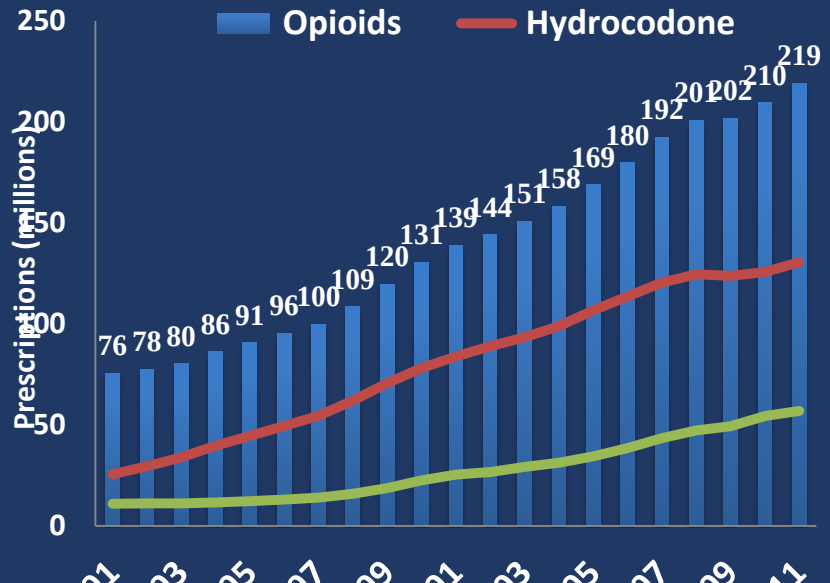


2017



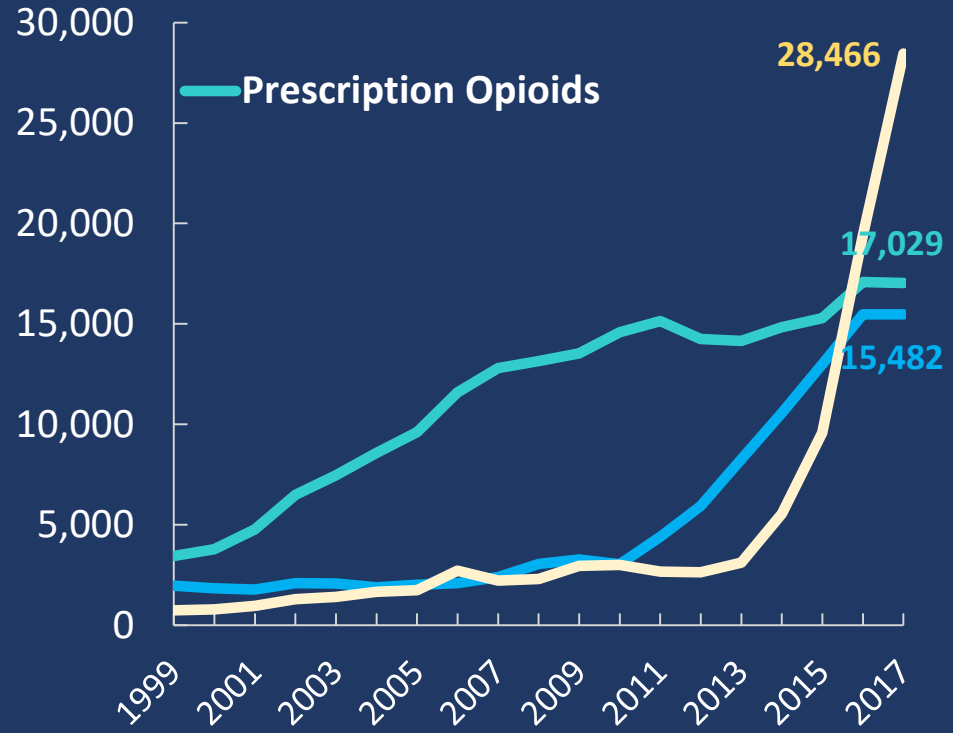
- **SOURCE:** National Center for Health Statistics, National Vital Statistics System, mortality data (http://www.cdc.gov/nchs/deaths.htm).
- **SUGGESTED CITATION:** Rossen LM, Bastian B, Warner M, Khan D, Chong Y. Drug poisoning mortality: United States, 2003–2017. National Center for Health Statistics. 2019. (Available from: https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/).

Opioid Prescriptions: 1991-2011

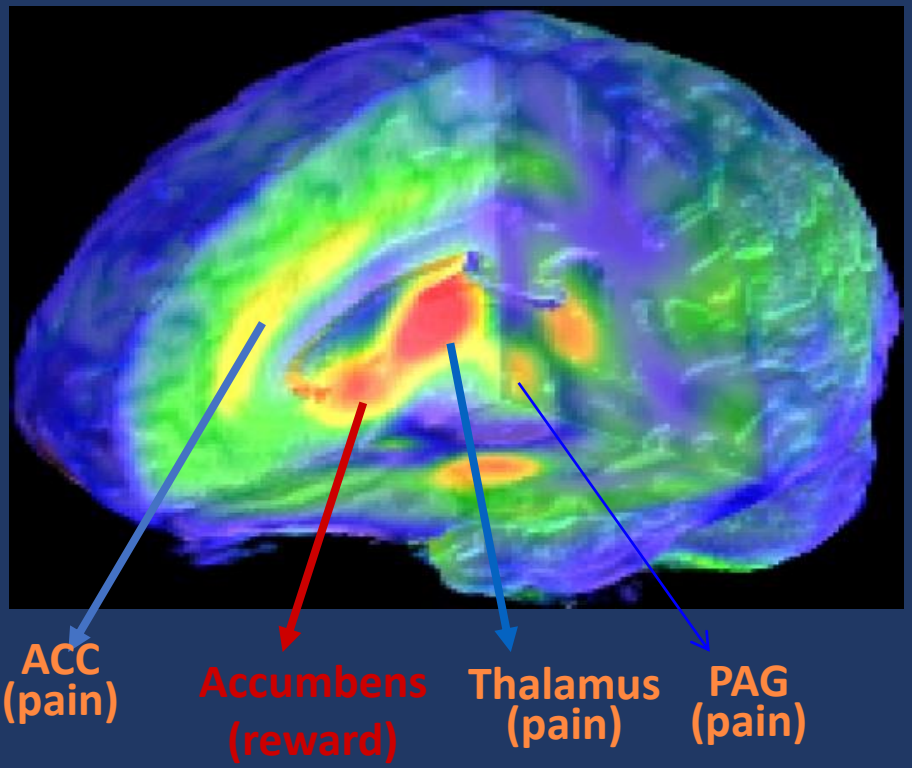


IMS's Source Prescription Audit (SPA) &…

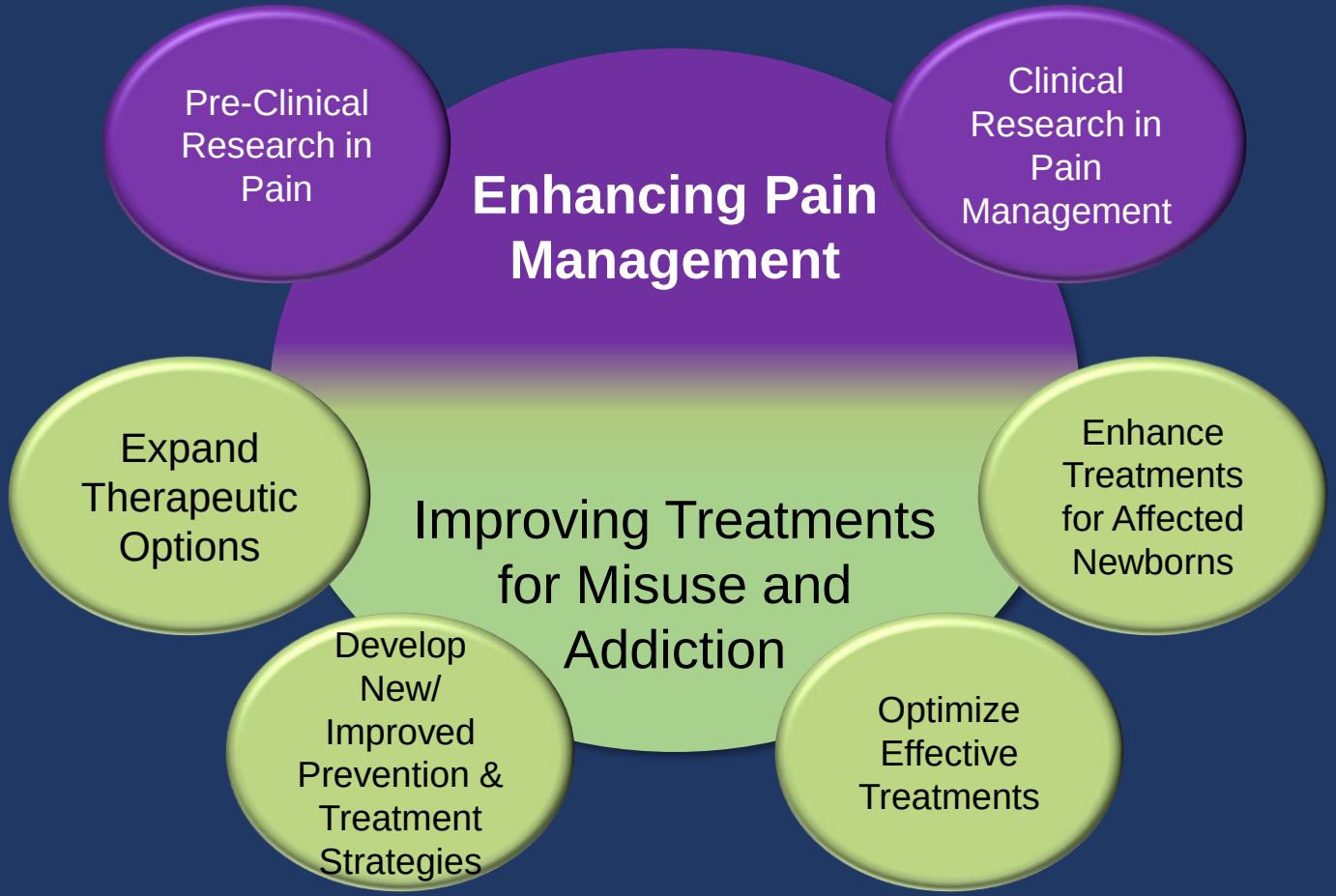
Waves Opioid Crisis: Overdose Fatalities



Analgesic & Reward Mechanisms of Mu Opiate Drugs (Heroin, Vicodin, Morphine)



HEAL Initiative Research Plans

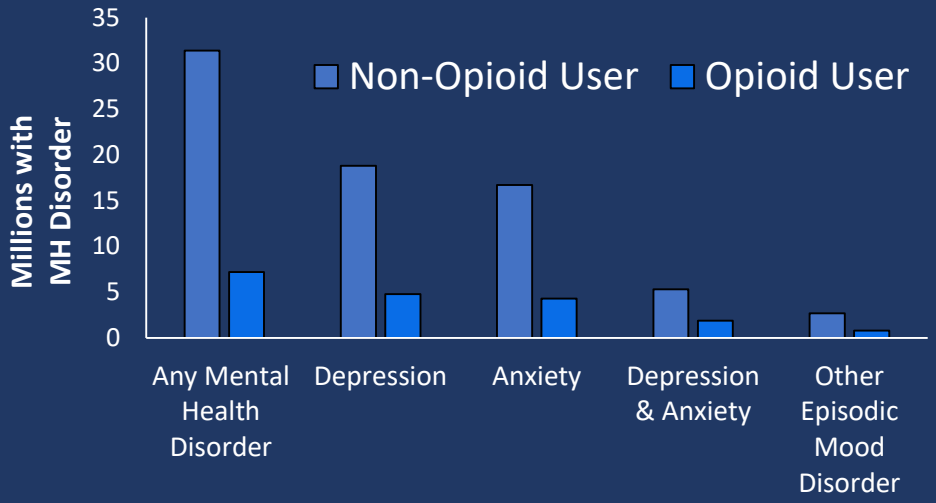


Advancing Fundamental Science

- Understand factors underlying vulnerability to pain conditions
- Biomarkers for pain
- Discover, validate novel targets for pain treatment

Understand factors underlying vulnerability to pain

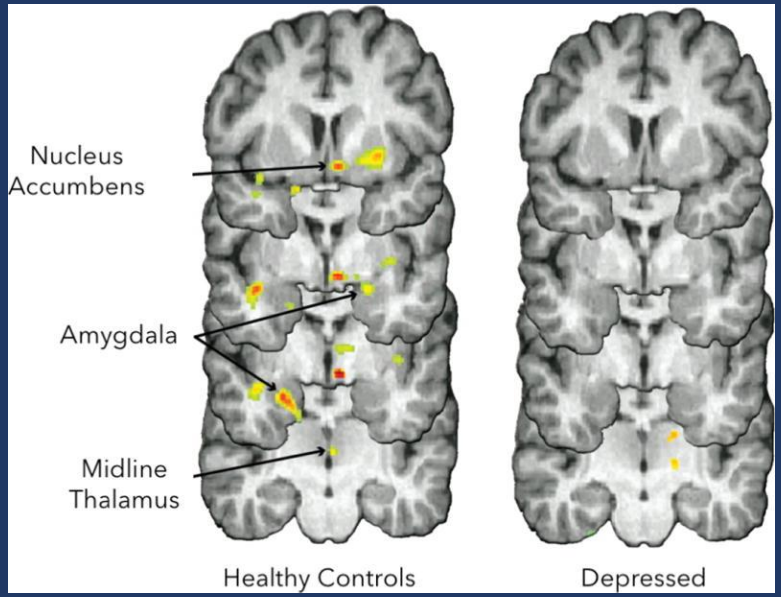
High Co-morbidity of Pain, Depression and Opioid Addiction



16% Adult Americans have a MH disorder (mostly mood disorders) and receive >50% of prescribed opioids

Davis MA et al., JABFM July–August 2017; 30(4).

MOR availability during social rejection



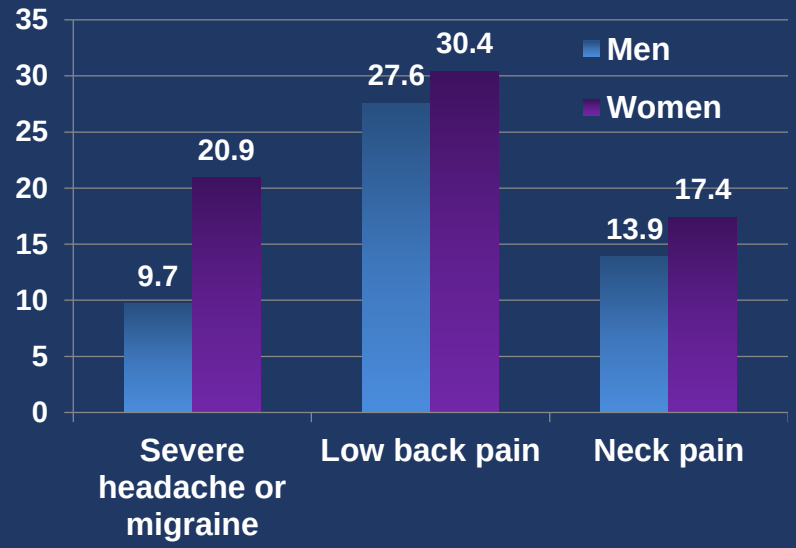
Depressed patients, did not show social rejection induced opioid release in accumbens, amygdala and mid-thalamus

Hsu et al., Mol Psychiatry.

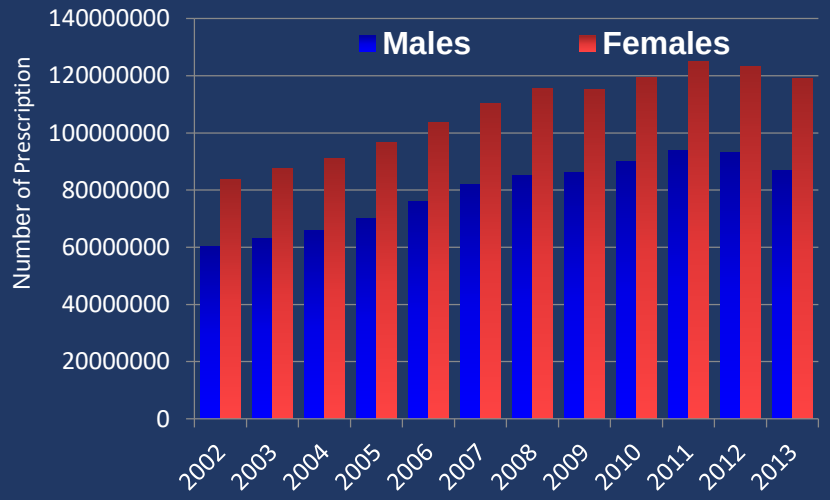
Understand factors underlying vulnerability to pain

Women Suffer More Pain Conditions and are Prescribed More Opioids

Rates of U.S. Adults > 18 and Older Reporting Pain, 2015



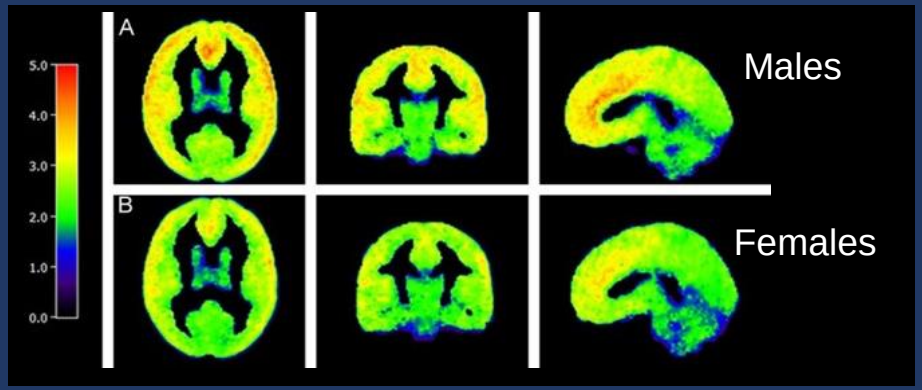
Opioid Prescriptions U.S. Retail Pharmacies

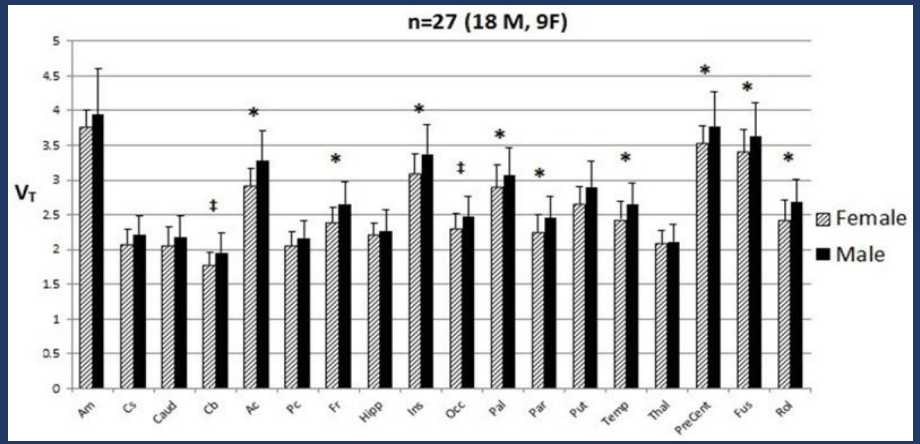


Source:CDC and NCHS, 2015

Source: IMS Health, National Prescription Audit

Gender Differences in Kappa Opioid Receptor Availability





- Lower Kappa receptor availability in females than males could reflect:
- Increased dynorphin, which is "mostly" aversive.
- Lower levels of Kappa receptors
- Could this contribute to gender differences in pain catastrophizing

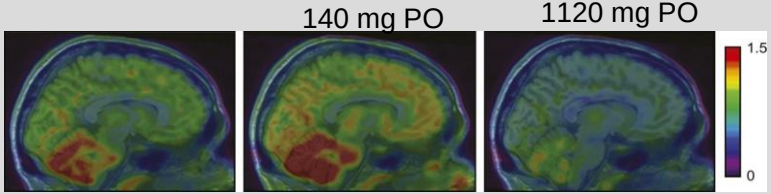
Vijay et al., Am J Nucl Med Mol Imaging. ***2016.***

Developing Biomarkers for Pain

Target Engagement

Targeting Calcitonin Gene-Related Peptide (CGRP) for migraine therapy

CGRP Occupancy by Telcagepant [^{11}C]MK-4232 and PET



*Therapeutic doses 140-280mg

<10 % occupancy *140 mg

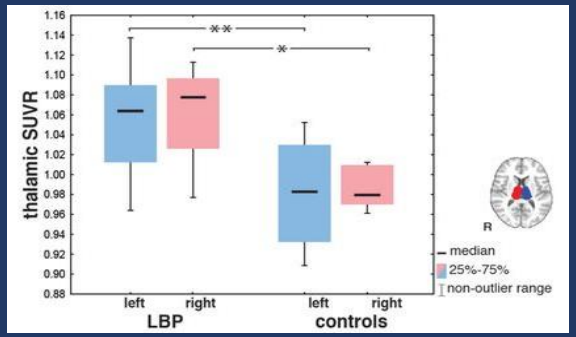
43-58% occupancy 1120 mg

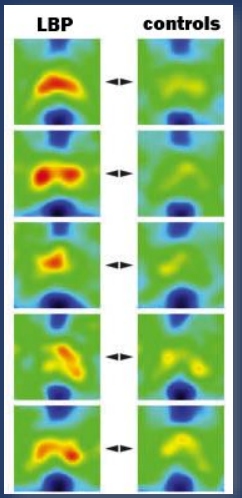
Hostetler et al. *J Pharmacol Exp Ther* 2013

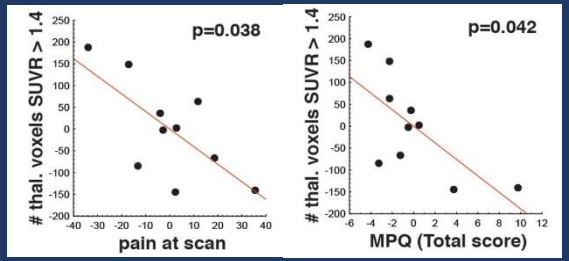
- Anti-CGRP peptide and anti-CGRP receptor antibodies are effective for preventing migraine.
- Telcagepant site of action is likely peripheral or via another receptor (AMY1 R *Walker et al., 2015*)

Biomarkers of Inflammation

Inflammation marker (PBR28) is Increased in Low Back Pain (LBP)





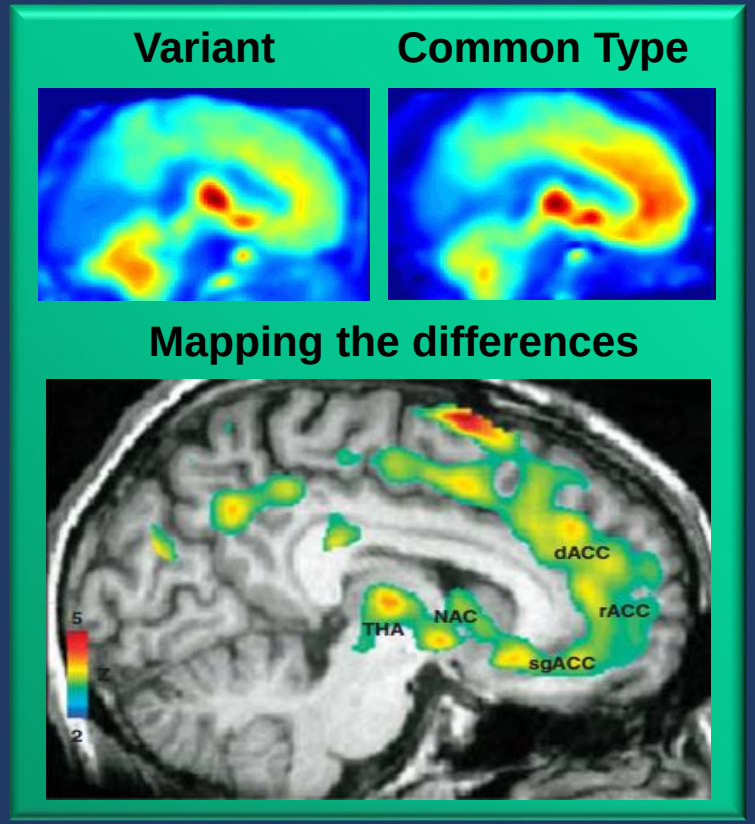


Thalamic PBR28 binding was inversely correlated with perception of pain

Loggia et al. Brain 2015;138

Biomarkers to Predict Addiction

- *OPRM1* encodes for target of opioids – and varies from person to person
  - *OPRM1* variant
  - Affects specific receptor levels in brain
  - Associated with increased risk for addiction, overdose severity
- Highlights *precise, personalized* nature of addiction….

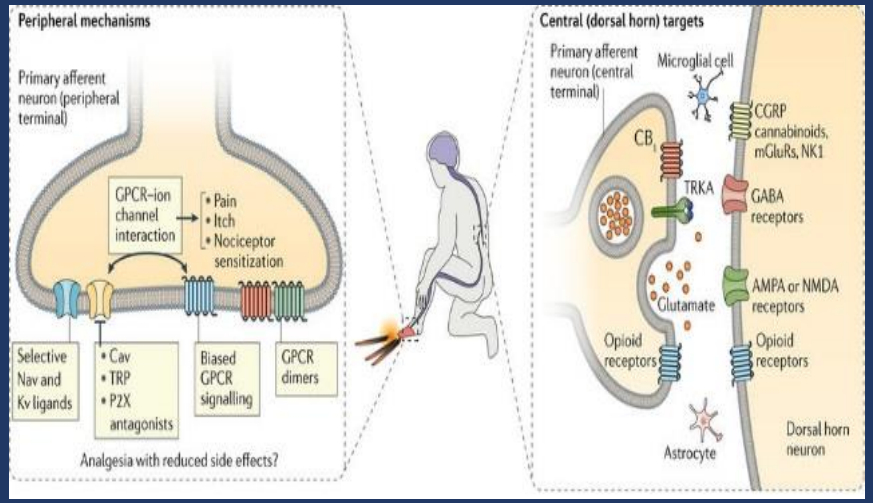


Hancock et al., *Biol Psychiatry* 2015; 78
Manini et al., *J Med Toxicol* 2013; 9

Peciña et al., *Neuropsychopharmacology* 2015; 40

Discover and Validate Novel Targets for Safe and Effective Pain Treatment

$Na_v1.7$ as a Potential Target For Potent Non-Addictive Analgesic



Nat Rev Drug Discov. 2017 Aug;16(8):545-564.

NATURE|Vol 444|14 December 2006

An *SCN9A* channelopathy causes congenital inability to experience pain

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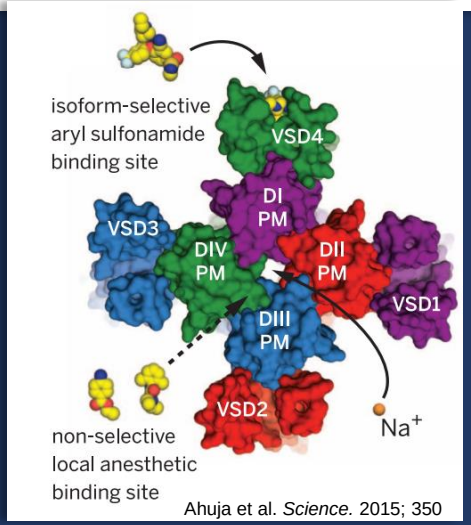
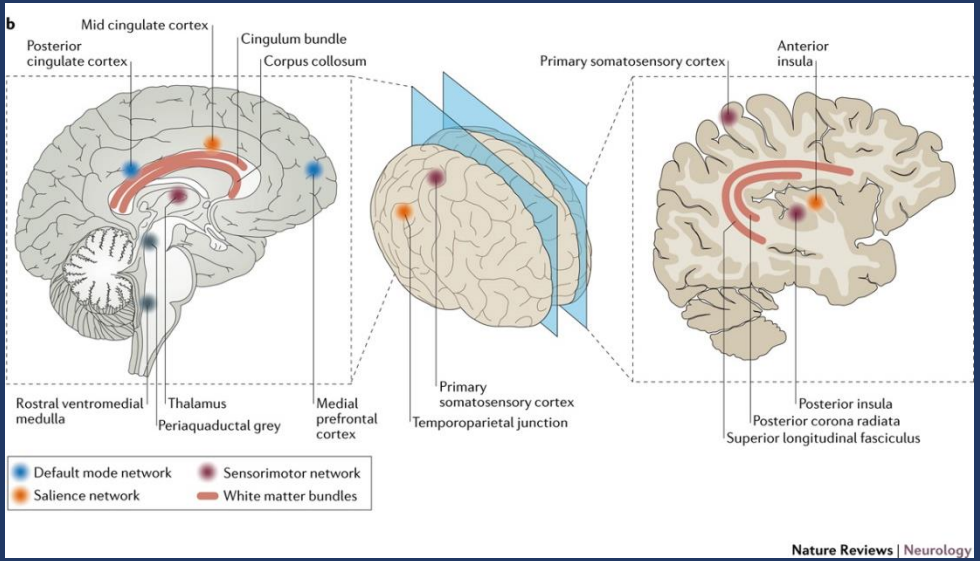
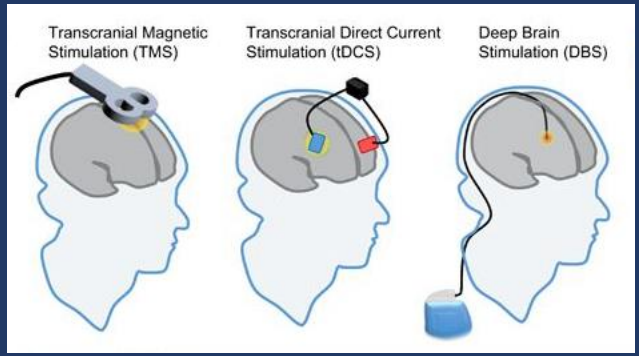


Ahuja et al. *Science.* 2015; 350

Neuromodulation for Pain





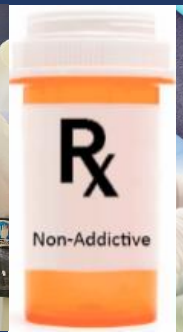
Brain areas showing abnormal resting state functional networks and white matter tractography in chronic pain.

Davis, K. D. et al. (2017) Nat. Rev. Neurol.2017

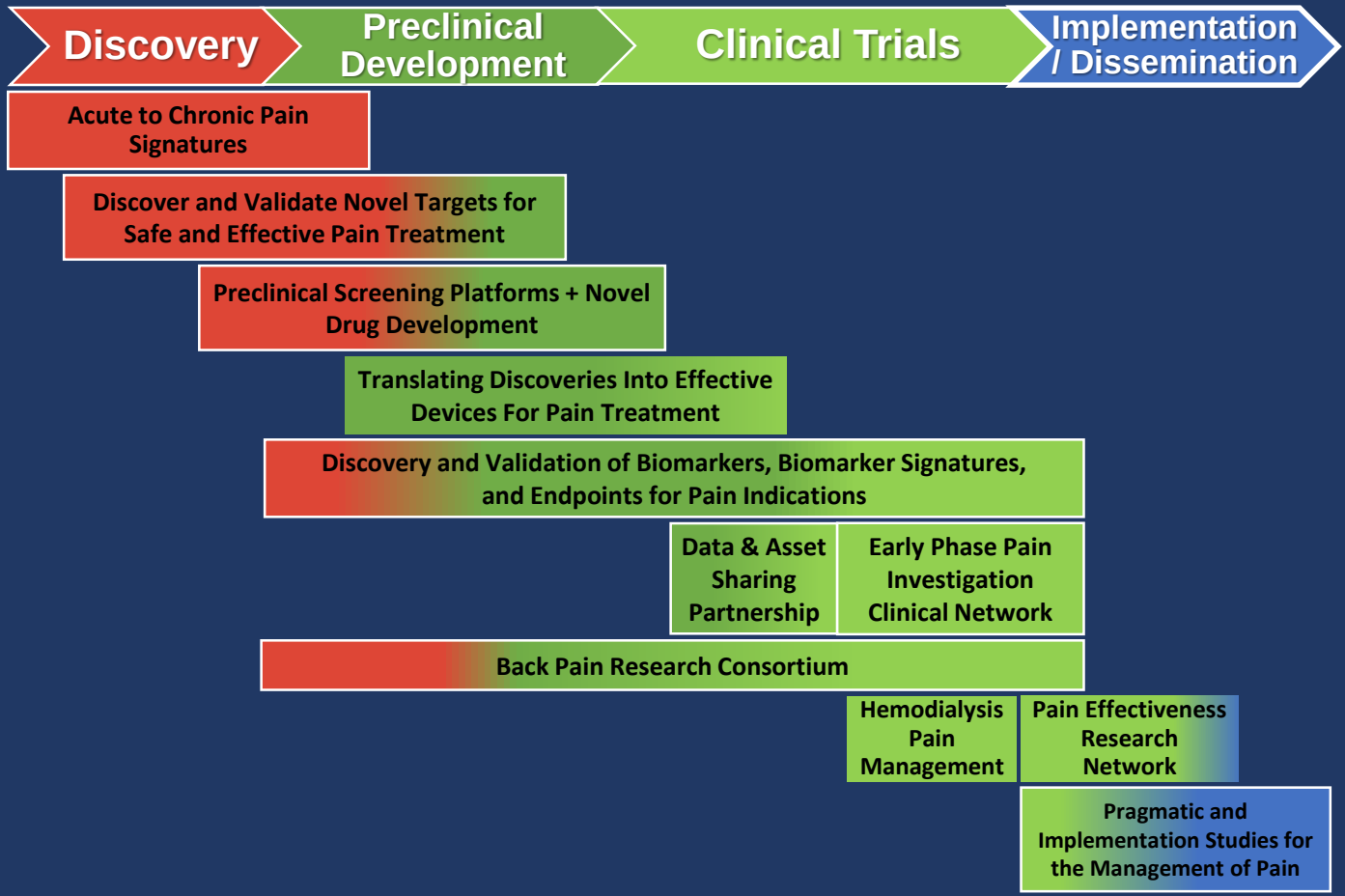
Enhancing Pain Management
Advancing Effective Treatments

- Establish clinical trials network to test wide range of strategies for management of multiple different pain syndromes
  - Drugs, biologics, natural products, devices, mind-body approaches, etc.
  - Industry agrees to make available dozens of promising pain treatments
- Develop ways to make pain management data more widely accessible
  - To speed clinical translation of what we've learned
  - To encourage formation of innovative partnerships





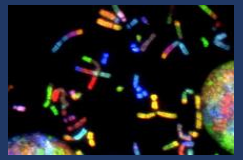
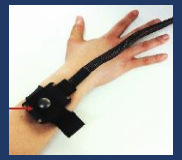
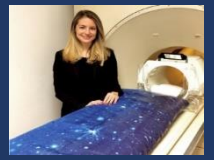

HEAL Programs for Pain Cover the Research Spectrum



Acute to Chronic Pain Signatures

- Objective biosignatures to identify susceptibility or resilience to chronic pain
  - Phenotyping
  - Genotyping
  - Sensory tests
  - Imaging
  - -omics
- Outcomes
  - Mechanisms
  - Novel therapeutic targets
  - Cohort stratification
  - Prevention




Structure:
- Clinical Coordination Center
- Clinical Centers
- Omics Data Generation Centers
- Data Integration and Resource Center

https:/comm/onfund.nih.gov/pain

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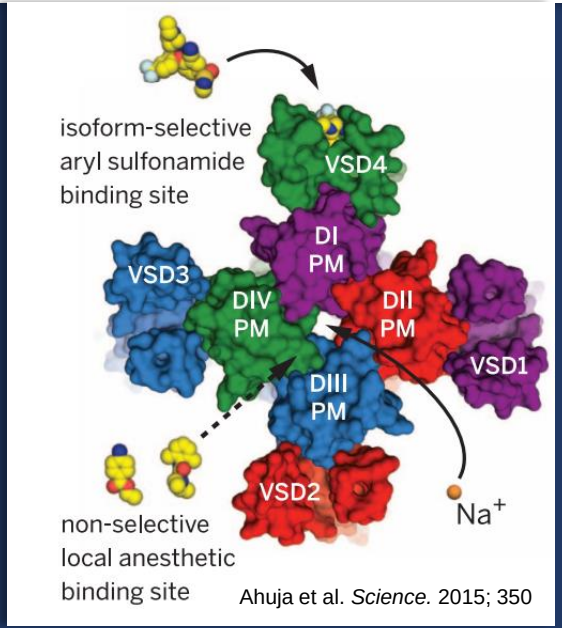

Ahuja et al. *Science.* 2015; 350

Surprisingly, many potent selective antagonists of Nav1.7 are weak analgesics

- Loss of Nav1.7 results in transcriptional upregulation of Penk (precursor of met-enkephalin) in DRG neurons.
- As opioid-dependent analgesia accounts for Congenital Insensitivity to Pain (CIP) phenotype (Naloxone restores sensitivity to pain), this identifies an endogenous opioid action with no tolerance
- In preclinical models of pain the combination of Nav1.7 blockade with very low dose buprenorphine or enkphalinase inhibitors produced dramatic analgesia

Emery et al., Expert Opinion Therapeutic Targets, 2017